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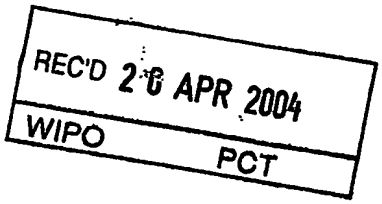

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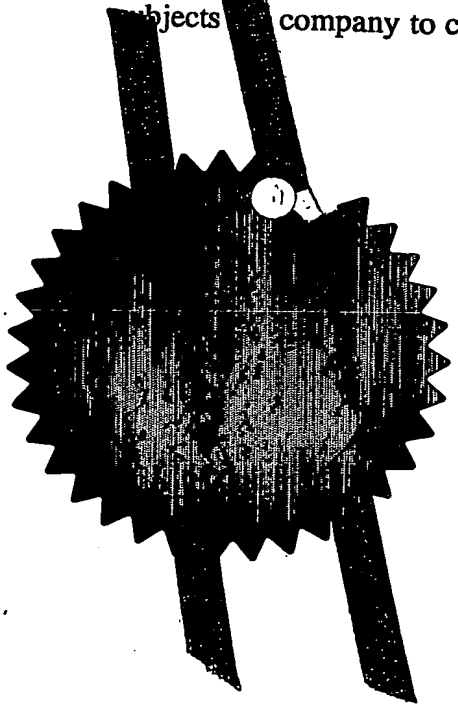
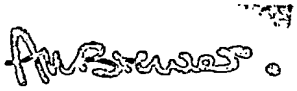


Signed 

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1. Your reference	MA/LTH/PB60164P
2. Patent application number *(The Patent Office will fill in his part)*	0307259.2 28 MAR 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, Great Britain
Patents ADP number *(if you know it)*	473587003
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4. Title of the invention	Process
5. Name of your agent *(if you have one)*	Corporate Intellectual Property
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Continuation sheets of this form	9
Description	2
Claim(s)	1
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11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 28-Mar-03

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

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PROCESS

The present invention is concerned with the maleate salt of the antidiabetic 5-[4-[2-(N-methyl-N-(2-pyridyl) amino)ethoxy]benzyl]thiazolidine-2,4-dione, which has the approved name rosiglitazone and more particularly with its production and isolation.

Rosiglitazone which is described and claimed in EPA 0306228 shows good blood glucose lowering activity and is useful for the treatment and or prophylaxis of hyperglycemia and of particular use in the treatment of Type II diabetes, hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

An improved process for the preparation of rosiglitazone is described and claimed in EPA 121 9620A1.

EP0658161B1describes the preparation and isolation of a maleate salt of rosiglitazone, which is hereinafter referred to as Compound 1. More particularly EP0558161B1 teaches that the maleate salt of rosiglitazone (Compound 1) may be prepared by dissolving rosiglitazone and maleic acid in hot ethanol, filtering the hot solution, allowing it to cool, and then filtering off the required salt which had then crystallised from the solution.

Subsequently three further polymorphs of rosiglitazone maleate were discovered and these are described in WO 00/64892, WO 00/64896 and WO 00/64893. These applications teach that Compound 1 may be prepared by dissolving each of the three polymorphs in hot denatured ethanol and then seeding with Compound 1. Thus WO 00/64893 teaches that Compound 1 may be prepared by dissolving the new polymorph described therein (and herein after referred to as the Form 4 polymorph) in hot denatured ethanol, filtering the hot solution into a preheated vessel (56°), heating the filtrate to 60°C, cooling with stirring, at 55°C seeding with the Compound 1 and then the cooling process continued.

For use in therapy the required pharmacuetical formulations of rosiglitazone are conveniently prepared using Compound 1 and therefore it is necessary that the process used for its manufacture is robust and consistently provides the desired product at a quality suitable for that use.

Prior to the preparation and isolation of the three additional polymorphs of rosiglitazone maleate the process described in EP0658161B1 consistently met the requirements for producing, on a manufacturing scale, the required Compound 1 of a quality suitable for pharmaceutical use.

Subsequent to the preparation and isolation of the three additional polymorphs it was found that the described process no longer provided a reliable method for the preparation of Compound 1 and it was necessary to develop a more robust process for preparing the required Compound 1 on a commercial scale. (More specifically the method described was found to generate the Form 4 polymorph)

We have now found that the required Compound 1 of a quality suitable for pharmaceutical use can consistently be prepared by crystallisation of rosiglitazone maleate, with or without seeding, in a solvent with a dielectric constant of less than 21. The present invention thus provides a process for preparing Compound 1 substantially free of other polymorphs, which comprises crystallising rosiglitazone maleate in a solvent with a dielectric constant of less than 21 or a mixture of solvents wherein at least one solvent has a dielectric constant of less than 21. Conveniently suitable solvents for use in the invention have a dielectric constant of less than 21. Suitable solvents for use in the crystallisation process include anisole, isopropyl acetate, ethyl acetate, dichloroethane, methyl isobutyl ketone, n-butanol, propan-2-ol, toluene, dimethyl carbonate, methyl ethyl ketone, acetone, or tetrahydrofuran or mixtures thereof. Further suitable solvents include mixtures of the abovementioned solvents (with dielectric constant <21) with other solvents, especially solvents with good solubility characteristics, for example ethanol, or denatured ethanol (Industrial Methylated Spirit [IMS]). For example suitable mixtures are

ethyl acetate and IMS, or toluene and IMS, or dimethyl carbonate and IMS Examples of suitable mixtures of solvents where both components have dielectric constant < 21 include dimethyl carbonate and acetone, or dimethyl carbonate and propan-2-ol.

A particularly useful solvent for use in this process is tetrahydrofuran.

The required solution of rosiglitazone maleate for use in the process may be obtained by heating rosiglitazone maleate in the chosen solvent, conveniently at a temperature of less than 70°C. Alternatively the required solution of rosiglitazone maleate may be obtained by combining rosiglitazone and maleic acid in the chosen solvent, conveniently at a temperature of less than 70°C

The process according to the invention is preferably carried out by filtering the hot solution through a pre-heated filter, cooling the filtrate and then isolating the required Compound 1.

The term substantially free as used herein refers to Compound 1 which preferably contains less than 10% of other polymorphs and more particularly no more than 5% of other polymorphs of rosiglitazone maleate.

The Compound I prepared according to the process of the invention being substantially free of any other polymorphs of rosiglitazone maleate is therefore suitable for pharmaceutical use.

In a further aspect the invention provides a process for preparing the Compound I essentially free of any other polymorphic forms of rosiglitazone maleate which comprises crystallising rosiglitazone maleate from a solvent or mixture of solvents with a dielectric constant of 14. Conveniently the solvent used in the crystallisation process have a dielectric constant of greater than 2.0 and less than 14.

Suitable solvents fo use in the crystallisation process include anisole, isopropyl acetate, ethyl acetate, dichloroethane, methyl isobutyl ketone or tetrahydrofuran or mixtures thereof.

A particularly useful solvent for use in this process is tetrahydrofuran

The required solution of rosigltazone maleate for use in the process may be obtained by heating rosiglitazone maleate in the chosen solvent, conveniently at a temperature of less than 70°. Alternatively the required solution of rosiglitazone maleate may be obtained by combining rosiglitazone and maleic acid in the chosen solvent, conveniently at a temperature of less than 70°C

The process according to the invention is preferably carried out by filtering the hot solution through a pre-heated filter, cooling the filtrate and then collecting the required Compound 1 by filtration . Conveniently the vessel collecting the filtrate is free of any contamination by any other polymorph and this may be achieved by washing procedures. The term essentially free as used herein means that the Compound1 does not contain any detectable levels of the other known polymorph forms of rosigiltazone maleate (i.e. less than 2%) when analysed by conventional techniques known for solid state analysis, conveniently X-ray diffraction techniques. More preferably the term 'essentially free' means that when the product of the process is used as seed material in a rosiglitazone maleate crystallisation (which without seeding would not furnish polymorphically pure Compound 1) the resultant Compound 1 also does not contain any detectable levels of any other polymorph when analysed by conventional solid state analytical procedures. Suitable solid state analysis procedures and techniques include infra red spectroscopy, X-ray diffraction techniques, Raman spectroscopy and Solid State Nuclear Magnetic Resonance. In particular, X-ray powder diffractometry and infra red spectroscopy including infra red spectroscopy with second differential processing are suitable techniques.

We have found that when Compound 1 essentially free of other polymorphs is used as seed material in the process for crystallisation of rosiglitazone maleate from a solution in a solvent with dielectric constant >21, eg ethanol e.g denatured ethanol, the product of this process is Compound 1 of a quality suitable for pharmaceutical use.

Further this process is not only robust but provides a particularly advantagous means for preparing Compound 1 of the required quality on a commercial scale.

Thus in a further aspect the invention further provides a process for preparing Compound 1 which comprises seeding a solution of rosiglitazone maleate in a suitable solvent with a dielectric constant > 21 with Compound 1 essentially free of other polymorphic forms prepared according to the invention.

Suitable solvents for use in this process include ethanol, denatured ethanol and methanol. In a preferred embodiment of this invention the process for preparing Compound 1 comprises seeding a solution of rosiglitazone maleate in denatured ethanol with Compound 1 seed material prepared according to the invention. Conveniently this process is carried out by heating the solution of rosiglitazone maleate in denatured ethanol to a temperature of less than 70°C eg 68-69°, adjusting the temperature of the filtrate to approximately 60°C cooling with stirring, then adding the seed material when the solution temperature is approximately 50° and then continuing the cooling to a temperature of less than 25°C and isolating the Compound1 by filtration.

The invention further provides a process for the preparation of Compound 1, essentially free from any other polymorph of rosiglitazone maleate which comprises crystallising rosiglitazone maleate from a solvent selected from anisole, isopropyl acetate, ethyl acetate, dichloroethane, acetone, methyl isobutyl ketone or tetrahydrofuran or mixtures thereof. The required solution of rosigltazone maleate for use in the process may be obtained by heating rosiglitazone maleate in the chosen solvent, conveniently at a temperature of less than 70°.

The process according to the invention is preferably carried out by filtering the hot solution through a pre-heated filter, cooling the filtrate and then collecting the required Compound 1 by filtration. Conveniently the vessel collecting the filtrate is free of any contamination with any other polymorph of rosiglitazone maleate and this may be achieved by conventional cleaning procedures.

A particularly useful solvent for use in this process is tetrahydrofuran

The following examples illustrate the invention but does not limit it in any way.

SECTION A:

Preparations of Compound 1(rosiglitazone maleate) essentially free of other polymorphs. Unless otherwise specified the rosiglitazone used as input material was Compound 1.

Example 1:

Rosiglitazone maleate (1.0 g) was added to anisole (200 ml) and the mixture was heated to 70°C, then filtered to remove undissolved material. The filtrate was reheated to 65°C and allowed to cool. The mixture was stirred for 2 hours at 20-25°C then filtered, the filter cake washed with diethyl ether (10 ml), and the solid dried in a vacuum oven to give Compound 1 (0.25 g, 25% recovery).

Example 2:

Rosiglitazone maleate (2.0 g) was added to isopropyl acetate (400 ml) and the mixture was heated to 75°C, then filtered to remove undissolved material. The filtrate was reheated to 65°C and allowed to cool. The mixture was stirred for 2 hours at 20-25°C then filtered. The filter cake washed with isopropyl acetate (10 ml), and the solid dried in a vacuum oven to give Compound 1 (1.32 g, 66% recovery).

Example 3:

Rosiglitazone maleate (2.0 g) was added to ethyl acetate (200 ml) and the mixture was heated to reflux, and the resulting solution was filtered. The filtrate was reheated to reflux and allowed to cool. The resulting suspension was stirred for 2 hours at 20-25°C then filtered. The filter cake washed with ethyl acetate (10 ml), and dried in a vacuum oven to give Compound 1 (1.58 g, 79% recovery).

Example 4:

Rosiglitazone maleate (5.0 g) was added to tetrahydrofuran (35 ml) and the mixture was heated to reflux, then filtered. The filtrate was reheated to reflux and allowed to cool. The mixture was stirred for 1.5 hours at 20-25°C then filtered. The filter cake washed with tetrahydrofuran (8 ml), and the solid dried in a vacuum oven to give Compound 1 (3.56 g, 71% recovery).

Example 5:

Rosiglitazone maleate (2.0 g) was added to dichloroethane (85 ml) and the mixture was heated to reflux, then filtered. The filtrate was reheated to 70°C and allowed to cool. An oil was originally produced which crystallised upon further cooling. The mixture was stirred for 2 hours at 20-25°C then filtered. The filter cake dried in a vacuum oven to give Compound 1 (1.67 g, 84% recovery).

Example 6:

Rosiglitazone maleate (2.0 g) was added to methylisobutyl ketone (240 ml) and the mixture was heated to 70°C, then filtered. The filtrate was reheated to 65°C and allowed to cool. Crystallisation commenced after 0.5 hours at 20-25°C - the mixture was stirred

for a further 1.5 hours at 20-25°C then filtered. The filter cake was washed with methylisobutyl ketone (15 ml), and dried in a vacuum oven to give Compound 1 (1.33 g, 67% recovery).

Example 7:

A mixture of rosiglitazone free base (6.0 g) and tetrahydrofuran (30 ml) was heated to 35°C, and maleic acid (2.10 g) was added. The resulting solution was heated to 60°C, held at this temperature for 20 min, then filtered. The filtrate was reheated to 60°C and allowed to cool. The mixture was stirred for 2 hours at 20-25°C then filtered. The filter cake washed with tetrahydrofuran (10 ml) and dried in a vacuum oven to give compound 1 (5.22 g, 66% yield).

Example 8:

Maleic acid (3.3 g) was added to a stirred suspension of rosiglitazone (10.0 g) in tetrahydrofuran (100 ml). The reaction mixture was stirred for 45 minutes at 21°C. The clear solution was filtered, reduced to 50 ml, then stirred for 17 hours at 21°C. The white solid was collected by filtration, washed with tetrahydrofuran (20 ml) then dried on the filter for 15 minutes to give the product as a white solid (11.65 g)

Example 9:

Maleic acid (0.33 g) was added to a stirred suspension of rosiglitazone (1.0 g) in diethyl ether (200 ml) at 21°C. The reaction mixture was stirred at reflux for 30 minutes, then cooled to 21°C. (A clear solution was not observed) The reaction mixture was stirred for 24 hours at 21°C, the white solid was collected by filtration, washed with diethyl ether (20 ml) then dried on the filter for 15 minutes to give the product as a white solid (1.1 g)

Example 10:

Rosiglitazone maleate, Form 4 polymorph (0.5 g) and tetrahydrofuran (10 ml) was stirred and heated to reflux until a clear solution was observed. The reaction was stirred for a further hour at reflux and then cooled to 21°C and stirred for 20 hours at 20°C. The white solid, Compund 1, was collected by filtration and washed with tetrahydrofuran (10 ml) then dried on the filter for 20 minutes.

B: Preparations of Compound 1 (rosiglitazone maleate) substantially free of other polymorphs

Example 11:

Rosiglitazone (3.33 g) in n-butanol (100 ml) was heated to 70°C for 15 minutes, then filtered. The solution was reheated to 70°C, then cooled to 20-25°C and stirred for 2 hours at 20-25°C. The white solid was collected by filtration, washed with IMS (8 ml) then dried at 50°C under vacuum for 24 hours to give the product as a white solid (2.74 g)

Example 12:

Rosiglitazone (4.0 g) in methyl ethyl ketone (120 ml) was heated to 65-70°C for 20 mins then filtered. The filtrate was reheated to 65°C, cooled to 20-25°C and stirred for 2.5 hours at 20-25°C. The solid was collected by filtration, washed with methyl ethyl ketone (15 ml) then dried under vacuum at 50°C for 18 hours to give the product as a white solid (2.42 g)

Example 13:

Maleic acid (0.33 g) was added to a suspension of rosiglitazone (1.0 g) in propan-2-ol (20 ml) at 21°C. The mixture was stirred for 25 minutes at an oil bath temperature of 60°C, then cooled to 21°C and stirred for 2 hours at 21°C. The white solid was collected by fiiltration, washed with IPA (10 ml) then dried on the filter for 10 minutes to give the product as a white solid (1.24 g).

Example 14:

Maleic acid (0.35 g) was added to a stirred suspension of rosiglitazone (1.0 g) in a mixture of IMS (10 ml) and toluene (25 ml) at 21°C under argon. The reaction mixture was heated at an oil bath temperature of 55°C for 30 minutes, then cooled to 21°C and stirred for 17 hours 21°C. The white solid was collected by filtration, washed with toluene (10 ml) then dried on the filter for 10 minutes to give the product as a white solid (0.91 g)

Example 15:

Maleic acid (0.33 g) was added to a stirring suspension of rosiglitazone (1.0 g) in a pre-mixed solvent of IMS:dimethylcarbonate (5 ml: 5ml) at 21°C under argon. The reaction mixture was heated at an oil bath temperature of 55°C for 20 minutes, then cooled to 21°C and stirred for 3 hours at 21°C. The white solid was collected by filtration, washed with IMS (20 ml) then dried on the filter for 20 minutes to give the product as a white solid (0.69 g)

Example 16:

Maleic acid (0.33 g) was added to a stirred suspension of rosiglitazone (1.0 g) in a pre-mixed solvent mixture of IMS: ethyl acetate (3 ml: 7ml) at 21°C under argon. The reaction mixture was heated at an oil bath temperature of 55°C for 30 minutes, then cooled to 21°C and stirred for 17 hours at 21°C. The white solid was collected by filtration, washed with IMS (20 ml) then dried on the filter for 15 minutes to give the product as a white solid (0.97 g)

C: Process to prepare Compound 1 substantially free of other polymorphs using suitable seed material

Example 17:

Maleic acid (0.33 g) was added to a stirred suspension of rosiglitazone (1.0 g) in IMS (30 ml). The reaction mixture was stirred at an oil bath temperature of 60°C for 22 minutes.

The hot solution was filtered, then seeded with the product of Example 8 (40 mg) and stirred for 2 hours at 21°C. The white solid was collected by filtration, washed with IMS (10 ml) and dried on the filter for 15 minutes to give the required product as a white solid (0.79 g).

Claims

1. A process for preparing the rosiglitazone maleate polymorph, Compound 1 substantially free of other polymorphs, which comprises crystallising rosiglitazone maleate in a solvent with a dielectric constant of less than 21 or a mixture of solvents wherein at least one solvent has a dielectric constant of less than 21.

2. A process as claimed in claim 1 wherein the solvent or at least one of the solvents has has a dielectric constant of less than 19.

3. A process as claimed in claim 1 or claim 2 wherein the solvent is selected from anisole, isopropyl acetate, ethyl acetate ,dichloroethane, methyl isobutyl ketone, n-butanol, propan-2-ol, toluene, dimethylcarbonate, or tetrahydrofuran or mixtures thereof.

4. A process as claimed in any of claims 1 to 3 wherein the crystallisation solvent is a mixture selected from a ethylacetate and IMS, toluene and IMS, dimethylcarbonate and IMS, dimethylcarbonate and acetone, or dimethylcarbonate and propan-2-ol

5. A process for preparing the Compound I essentially free of any other polymorphic forms of rosiglitazone maleate which comprises crystallising rosiglitazone maleate from a solvent or mixture of solvents with a dielectric constant of less than 14.

6. A process as claimed in claim 5 wherein the solvent has a dielectric constant of greater than 2.8 and less than 14.

7. A process as claimed in claim 5 or 6 wherein the solvent is tetrahydrofuran.

8. A process for preparing Compound 1 which comprises seeding a solution of rosiglitazone maleate in a suitable solvent with a dielectric constant > 21, with Compound 1 essentially free of other polymorphic forms prepared according to the process as claimed in claims 5 and/or 6.

9. A process as claimed in claim 8 wherein the solvent is denatured ethanol

10. The use of Compound 1 essentially free of other polymorphs, prepared by the process of claims 5 and/or 6, as a seed material in a crystallisation process for preparing Compound 1 substantially free of other polymorphs of rosiglitazone maleate.

11. A process for preparing the Compound I essentially free of any other polymorphic forms of rosiglitazone maleate which comprises crystallising rosiglitazone maleate from a solvent or mixture of solvents selected from anisole, isopropyl acetate, ethyl acetate , dichloroethane, acetone, methyl isobutyl ketone or tetrahydrofuran.

ABSTRACT

A crystallisation process for preparing a polymorph of rosiglitazone maleate (Compound 1), and a process for preparing Compound 1 with a polymorphic purity that is suitable for use as a seed material in a crystallisation process for preparing Compound 1.